Prenatal Alcohol Exposure: Effects on Brain Structure and Function

Fetal Alcohol Syndrome (FAS), a devastating developmental disorder resulting from heavy maternal alcohol consumption during pregnancy, was first identified in France in 1968 (Lemoine et al. 1968) and in the United States in 1973 (Jones et al. 1973). FAS can be readily diagnosed shortly after birth when characteristic facial features and growth retardation are present, coupled with known prenatal alcohol exposure. Not as obvious at birth—but with more serious, pervasive, and lifelong consequences—are the effects of alcohol-induced damage to the developing brain and spinal cord, or central nervous system (CNS). Problems that become apparent later include reductions in general intellectual functioning and academic skills as well as deficits in verbal learning, spatial memory and reasoning, reaction time, balance, and other cognitive and motor skills. Some deficits, like problems with social functioning, appear to worsen as these individuals reach adolescence and adulthood, possibly leading to an increased rate of mental health disorders.

A greater understanding of both the structural damage to the CNS from alcohol exposure (the "neuroanatomical" effects) and the resulting behavioral manifestations (the "neurobehavioral" effects) will be critical to future research on effective therapies for FAS. In recent years, the principal advances have occurred in three areas: (1) the introduction of a new diagnostic system for categorizing fetal alcohol effects, (2) neuroimaging studies that have provided insights into the structural damage to the brain from prenatal alcohol exposure, and (3) the delineation of specific patterns of behavioral impairment in children with FAS. Each of these is described in this section.

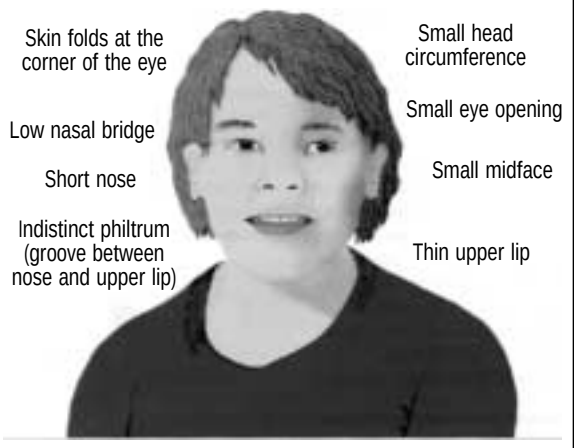
Diagnosing the Effects of Prenatal Alcohol Exposure

Researchers first outlined the diagnostic criteria for FAS in 1973 (Jones and Smith 1973; Jones et al. 1973). Although the terms used to describe the condition have changed over the years, the criteria for its diagnosis—growth deficiency, CNS dysfunction, and characteristic facial defects—have remained essentially the same.

Perhaps the most immediately obvious of alcohol's effects on the fetus is a pattern of abnormal facial features (figure 1) (Jones et al. 1973; Stratton et al. 1996). Although these facial abnormalities are a hallmark of FAS, they are not present in all children who have been exposed to alcohol before birth. More subtle neuroanatomical and neurobehavioral problems often occur in alcohol-exposed children without these facial abnormalities.

At one time, FAS was not diagnosed without confirming the mother's alcohol use during pregnancy. Unfortunately, this requirement resulted in many cases of prenatal alcohol exposure being overlooked or ruled out, especially when the child did not have the facial abnormalities of FAS. Another term, "fetal alcohol effects" (FAE), has been used for many years to describe individuals known to be exposed to alcohol before birth who

Figure 1: Facial features of FAS



Source: Gordis 1991.

Table 1: Criteria for diagnosing the effects of prenatal alcohol exposure

Diagnosis	Diagnostic criteria: FAS facial features	Diagnostic criteria: Confirmed prenatal alcohol exposure	Diagnostic criteria: Additional criteria
Fetal Alcohol Syndrome (FAS) with confirmed maternal alcohol exposure	Yes	Yes	
FAS without confirmed maternal alcohol exposure	Yes	No	Growth retardation; central nervous system (CNS) abnormality; or evidence of a behavioral or cognitive disorder inconsistent with the expected developmental level, with hereditary factors, or with the environment
Partial FAS with confirmed maternal alcohol exposure	Some	Yes	
Alcohol-related birth defects (ARBD)	No	Yes	Any of a number of anomalies (such as heart or kidney defects) present at birth that are associated with maternal alcohol consumption during pregnancy
Alcohol-related neurodevelopmental disorder (ARND)	No	Yes	Evidence of CNS abnormality (such as an abnormally small head, abnormal brain structures, and neurological signs); evidence of a behavioral or cognitive disorder inconsistent with the expected developmental level, with hereditary factors, or with the environment; or both

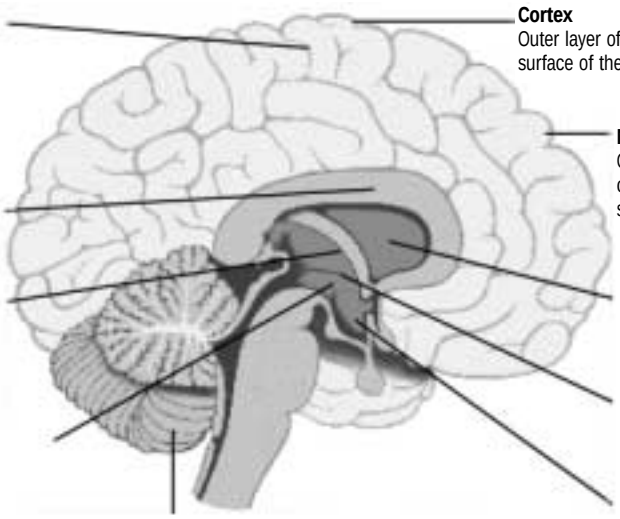
Source: Stratton et al. 1996. Reprinted with permission from *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Copyright 1996, National Academy of Sciences, Washington, DC.

do not have the FAS facial features but who do have other critical hallmarks of FAS (Clarren and Smith 1978). Of late, however, new diagnostic criteria and terminology have come into use.

A 1996 report sponsored by the Institute of Medicine (IOM) of the National Academy of Sciences classifies the effects of prenatal alcohol exposure into five categories (table 1) (Stratton et al. 1996). The IOM scheme includes three categories for individuals with all or some of the FAS facial features and two categories for alcohol-affected children without FAS facial features: "alcohol-related birth defects" (ARBD) and "alcohol-related neurodevelopmental disorder" (ARND).

The diagnoses of ARBD and ARND require confirmation of the mother's alcohol use during pregnancy in addition to a psychological or neurological assessment of the child. Without the facial features of FAS, however, these two classifications are the most difficult to characterize. Researchers will need to conduct large studies of children with these diagnoses in order to link specific physical and functional differences to prenatal alcohol exposure, and thus better define these two categories. In addition, the use of labels such as ARND indicates that psychological or neurological assessments are part of the diagnostic process, which is only now becoming more of the norm rather than the exception.

Figure 2: Anatomy of the brain



Source: Mattson et al. 1994a.

Neuroimaging: Precise Pictures of Structural Damage to the Brain

For many years, information on the neuroanatomical effects of prenatal alcohol exposure came from autopsies of children with FAS (Clarren 1986; Mattson and Riley 1996). Autopsied brains showed widespread and severe damage that included the following (figure 2):

- Malformations of the brain tissue (both in the "gray matter" regions, which contain mostly nerve cell bodies and extensions called dendrites, and in the "white matter" regions composed primarily of nerve fibers, or axons, that transmit impulses).

- Failure of certain brain regions to develop at all (such as the corpus callosum, the central tract inside the brain that unites the left and right hemispheres).

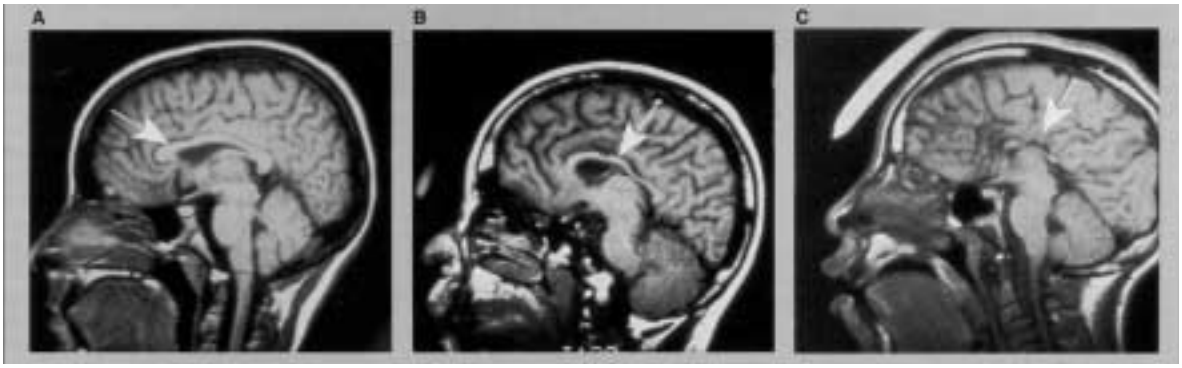
- Failure of certain cells to migrate to their appropriate locations during embryonic brain development.

- A tendency for the tissue to die off in other brain regions (such as the cerebellum, a region at the base of the brain that coordinates body movements).

The extent of these abnormalities initially led researchers to conclude that there was neither a specific pattern of brain changes nor a consistent behavioral profile among children exposed to alcohol prenatally (Clarren 1986).

In the decade since that conclusion, however, the use of neuroimaging techniques to visualize the living brain has provided a more precise picture of the brain structure of children with FAS. Using magnetic resonance imaging (MRI) and computed tomography, which measure the area or volume of a body structure, researchers have documented reduced overall brain size in children with FAS (Mattson et al. 1994*b*, 1996*c*). Several brain structures appear to be especially sensitive to prenatal alcohol exposure (Mattson and Riley 1996), whereas others do not seem to be affected at all. These findings suggest that alcohol exposure may be specific, rather than global,

Figure 3: Effects on the corpus callosum



(A) Magnetic resonance imaging showing the side view of a 14-year-old control subject with a normal corpus callosum; (B) a 12-year-old with Fetal Alcohol Syndrome and a thin corpus callosum; and (C) a 14-year-old with Fetal Alcohol Syndrome and agenesis (absence due to abnormal development) of the corpus callosum.

Source: Mattson et al. 1994a.

in its teratogenicity, or ability to cause developmental abnormalities.

Several MRI studies of children with FAS confirmed a link between prenatal alcohol exposure and anatomical defects at the midline of the brain and face (Johnson et al. 1996; Mattson et al. 1992; Riley et al. 1995; Swayze et al. 1997). The areas affected included those surrounding the fissure between the two sides of the brain, particularly the corpus callosum, which is sometimes missing (figure 3) (Johnson et al. 1996; Mattson et al. 1992; Riley et al. 1995; Swayze et al. 1997). The high incidence of anomalies in the middle of the brain suggests that this area is particularly sensitive to alcohol exposure before birth. Because specific regions of the brain are associated with certain physical and mental behaviors, data showing such region-specific effects may lead to a greater understanding of the behavioral manifestations of FAS.

Cerebellum

The cerebellum appears to be especially affected by prenatal alcohol exposure. This structure is located at the back of the brain and is thought to be involved primarily in movement, but also in cognitive processes such as attention. Case studies (Riikonen 1994; Robin and Zackai 1994) and autopsy reports (Clarren 1986; Mattson and Riley 1996) have identified smaller size and other abnormalities of the cerebellum in alcohol-exposed children with and without FAS. A recent imaging study has also revealed volume reductions in the cerebellum and has suggested that this structure is affected more than other brain regions by prenatal alcohol exposure (Harris-Collazo et al. 1998).

Another recent study examined changes in an area of the cerebellum called the vermis, which connects the two halves of the cerebellum (Sowell et al. 1996). The researchers found that 5 of 10 mapped regions in the vermis were significantly smaller in children who were exposed to alcohol prenatally than in those who were not. It is not entirely clear what behaviors are correlated with the cerebellar vermis, but there may be some relationship to gross motor functioning (such as balance) and attention.

Research suggests that the death of certain types of cells in the cerebellum may be responsible for its reduced size. These specialized cells, called Purkinje cells, send out nerve signals in response to sensory and motor impulses from the rest of the nervous system. A study in rats demonstrated that those animals exposed to alcohol shortly before or after birth (correlating with the third trimester of pregnancy in humans) had fewer Purkinje cells in some regions of the cerebellum than did nonexposed animals (Goodlett et al. 1990).

Basal Ganglia

The basal ganglia are paired masses of gray matter located deep within the white matter of the cerebrum. They include a structure called the caudate nucleus, which governs voluntary movement and some cognitive functions related to perception, thinking, and memory.

Two recent studies of children with FAS found significant reductions in the volume of the basal ganglia (Harris-Collazo et al. 1998; Mattson et al. 1996*c*). The results confirmed earlier findings that, even when reductions in overall brain size are accounted for, the basal ganglia (and especially the caudate nucleus) are significantly smaller in children exposed to alcohol before birth (Mattson et al. 1992, 1994*b*).

Other Brain Regions

In some areas of the brain, the effects of prenatal alcohol exposure may be minimal or nonexistent. This possibility has been strengthened by results from a recent neuroanatomical study in which researchers analyzed the "mean proportional volume"—the average volume of any given region in relation to overall brain size—of the four regions of the cerebral cortex (the thin outer layer of gray matter covering the surface of the cerebrum) (Harris-Collazo et al. 1998). The researchers found no significant differences between individuals with and without FAS, matched for age, in the mean proportional volume of the cerebral cortex and certain underlying regions (including the thalamus, basomesial diencephalon, substantia nigra, insula, and nucleus accumbens). Also unaffected were the brain areas that make up the limbic system (the hippocampus, parahippocampus, amygdala, and cingulate), which is associated with emotions and certain aspects of memory. These preliminary data need confirmation, however, especially since the number of subjects was small in this study. Size differences between segments of the brain may become evident as larger numbers of people are studied.

In addition to using imaging technologies, researchers have used population-based epidemiologic methods to add to the knowledge of how prenatal alcohol exposure affects the development of CNS structures. In a study of premature infants, researchers found that alcohol exposure was related to bleeding within the brain as well as damage to the brain's white matter (Holzman et al. 1995). Specifically, this risk was higher in premature infants of women who had had at least seven alcoholic drinks per week or at least three alcoholic drinks per occasion during their pregnancies. Another study investigated alcohol use by parents and defects of the neural tube, the embryonic structure that becomes the brain and spinal cord (Shaw et al. 1996). The results indicated that parental alcohol use was not associated with an increased risk for neural tube defects in their infants.

Physical Measures of Altered Brain Function: Cry Patterns and EEG's

Although pinpointing the structural changes in the brain provides important, dramatic evidence of alcohol-induced damage, it is equally important to quantify the resulting changes in function. If the alcohol-induced changes in brain function could be identified very early in a child's life, it might be possible to mitigate some of the adverse consequences as the child grows. Such identification efforts are hampered, however, by the difficulty in making diagnoses in the absence of FAS facial features and in measuring neurobehavioral effects at very young ages. Two lines of research have used tools that physically measure changes in brain function and may help in diagnosing and determining the prognosis for alcohol-exposed children who do not have the FAS facial features: acoustic analyses of babies' cry patterns, and electroencephalography (EEG) evaluations of brain electrical activity.

Acoustic Cry Analyses

By performing acoustic analyses of babies' cry patterns, researchers have detected subtle alcohol-related changes in neurobehavior in infants (Nugent et al. 1996; Zeskind et al. 1996). The characteristics of an infant's cry, which are at least partly determined by the CNS, can be affected by prenatal exposure to alcohol and other drugs. In one study of 3-day-old infants, researchers examined three characteristics of the crying of

babies with and without prenatal alcohol exposure: (1) threshold, or the intensity at which a stimulus provokes crying; (2) latency, or the time between the stimulus and the infant's cry; and (3) pitch, or the highness or lowness of the cry (Zeskind et al. 1996). The researchers discovered that all three of these characteristics differed significantly between the two groups of infants. Moreover, the differences were related to the amount of alcohol consumed by the mother during her pregnancy.

In another study, the same three cry characteristics were compared at 2, 14, and 28 days of age in alcohol-exposed infants and in control group infants (Nugent et al. 1996). The researchers found a number of significant differences between the two groups. The crying threshold was greater in the alcohol-exposed infants than in the nonexposed infants at 2 days of age, the cry latency of the alcohol-exposed infants was longer at 14 days, and the average pitch of the cries was higher among the control infants at day 2 but was higher among the alcohol-exposed infants at days 14 and 28.

Although these studies indicate that prenatal alcohol exposure interferes with subtle aspects of neurobehavior, researchers have yet to determine how differences in cry characteristics may relate to later neurobehavioral outcomes, such as learning or attention. Studies of other babies with health problems, such as those born prematurely, suggest that there is such a relationship (see Nugent et al. 1996). If this can be confirmed, it may be possible to use analysis of cry patterns to predict the later neurobehavioral effects of prenatal alcohol exposure.

EEG's

Investigations using EEG, which records the brain's electrical activity, suggest that EEG and neurological testing could help to identify less severe effects of alcohol exposure, such as ARND. Researchers used EEG measurements to compare children with FAS, children with Down syndrome, and normally developing control subjects (Kaneko et al. 1996*a,b*). Children with Down syndrome were included to rule out electrical patterns related to mental retardation. In the first of these studies, EEG was used to measure alpha waves, which are emitted by the brain when the body is in a state of deep relaxation (but not sleep) (Kaneko et al. 1996*b*). The EEG recordings found lower alpha wave activity in both the FAS and the Down syndrome children than in the control subjects. The characteristics of the alpha wave patterns differed, however, in that those of the Down syndrome children were slower, whereas those of the FAS children were weaker, than those of the control group children. Also, the reduced activity in the FAS children was found mainly in the left hemisphere of the cerebral cortex, whereas in the Down syndrome children it was mainly in the posterior cerebral cortex. These data suggest that the effects of prenatal alcohol exposure may specifically target the brain's left hemisphere and that they differ from the effects of other congenital disorders.

In a second study, neurological responses were recorded in the same group of children as they listened to sounds of various qualities and frequencies (Kaneko et al. 1996*a*). Researchers observed a delayed response in the brains of children with FAS and in the brains of those with Down syndrome. As in the previous study (Kaneko et al. 1996*b*), the region of the brain that was affected in the FAS children differed from the brain region affected in the Down syndrome group. These studies on brain activity indicate that children with prenatal alcohol exposure and children with Down syndrome have distinct profiles of brain electrical and neurological activity.

Effects on Cognitive and Motor Functions

Much of the research on the effects of prenatal alcohol exposure has focused on overall intellectual functioning, as measured by intelligence quotient (IQ) scores. In recent years, studies have turned to more specific aspects of brain functioning and behavior. Two broad assessments of neuropsychological functioning in preschool (Janzen et al. 1995) and school-age (Mattson et al. 1998) children found that children with FAS, as well as alcohol-exposed children who did not meet all the FAS criteria, had deficits in numerous areas. The most prominent of these

deficits were in integrating visual information with coordinated movements, controlling precise movements (for example, speed and coordination of finger movements), language, and general intellectual functioning. As described below, researchers have pursued the details of these deficits in recent years, focusing on learning and memory, visual-spatial functioning, executive functioning, attention, and motor control.

Although it is well established that heavy prenatal alcohol exposure leads to neurobehavioral impairment, the effects of lower levels of alcohol exposure are not as clear (National Institute on Alcohol Abuse and Alcoholism 1997). It appears that many of the problems linked to FAS also are found in children whose mothers drank moderate amounts of alcohol when pregnant, including deficits in general intellectual functioning (Larroque et al. 1995), visual-spatial reasoning (Hunt et al. 1995), attention (Jacobson et al. 1994; Streissguth et al. 1994*b*, 1995), and academic achievement (Goldschmidt et al. 1996; Streissguth et al. 1994*a*). In contrast, studies have found no effects of low alcohol exposure on gross motor functioning in young children (Chandler et al. 1996; Fried and Watkinson 1990; Richardson et al. 1995).

Learning and Memory

To assess learning and memory in children with and without FAS, researchers gave the children a standardized test (the California Verbal Learning Test–Children's version [CVLT–C]), which showed differences in immediate recall, delayed recall, and recognition of words that had been read aloud (Mattson et al. 1996*b*).

The children in this study were read a list of words and then asked to recall them immediately afterward and again after 20 minutes had passed. The children with FAS had difficulty recalling the words immediately after hearing them. After the 20-minute delay, they recalled fewer words than did the control group subjects. The FAS children also tended to offer words not on the list and to repeat words when trying to remember those on the list. When they were given a choice of words, the children with FAS had difficulty identifying which were on the original list and which were not. They also more often incorrectly identified words as being on the list. There were, however, no differences between the FAS and the control group in the percentage of the learned words they were able to recall after 20 minutes. In other words, the FAS children did not learn as many words as the control group children did, but the rate at which words were forgotten was the same in both groups.

The findings suggest that children with FAS have profound deficits in learning when material is presented verbally but are capable of retaining the information they learn. Similar results were obtained among children with prenatal alcohol exposure but without a diagnosis of FAS (Mattson et al. 1998).

In a study of implicit memory—the unconscious recall of a previously performed task—comparisons were made among children with heavy prenatal alcohol exposure (including FAS), children with Down syndrome, and normally developing children (Mattson and Riley 1999). The children, aged 8 through 17 years, studied a list of words that were both written and read aloud by an examiner. When asked what words they remembered from the list, the alcohol-exposed children could not name as many as the control group. But when asked which of two words they remembered (one on the list and one not), the two groups of children performed similarly.

In that same study, the children were also asked to fill in the missing letters of words from the list they had just studied (for example, "sm___ = small, mo____ = mother"). The alcohol-exposed group and the control group correctly completed the same number of these words. These findings suggest that the two groups of children were equally able to use previously learned information without being told to do so. In contrast, the children with Down syndrome were impaired on all three memory tasks. Overall, these findings suggest that prenatal alcohol exposure does not impair some types of memory, and that despite some learning deficits, children with FAS are able to retain learned information.

Visual-Spatial Functioning

The ability of persons with FAS to see objects and understand their spatial relationships, or "visual-spatial functioning," has received little research attention to date. The studies conducted thus far suggest that alcohol-exposed children have deficits in specific aspects of visual-spatial processing. In one of these studies, children with FAS were presented with a group of objects and later asked to recall them (Uecker and Nadel 1996). The children could remember what the objects were, but they had more trouble than the control group children in remembering the objects' locations in relation to each other. In addition, after 24 hours, the children with FAS had greater difficulty than the other children in remembering both the objects and their relative locations.

In another study, children with prenatal alcohol exposure were asked to remember certain figures composed of both large, simple shapes and small details (Mattson et al. 1996*a*). When the children tried to recreate the figures, their drawings lacked detail. The results of both of these studies suggest that alcohol-exposed children have problems in perceiving and remembering spatial relationships and in recalling visual details (Mattson et al. 1996*a*; Uecker and Nadel 1996). More research is needed to further define the nature of these deficits.

Executive Functioning

Higher order cognitive processes called "executive functions" are activities that require complex thought processes and behaviors, such as planning, organizing, sequencing, and other forms of abstract thinking. These are abilities that allow successful "independent, purposeful, self-serving behavior" (Lezak 1995). Persons with deficits in these areas may have difficulty with self-care and independence. For example, routine activities that require a sequence of steps, such as getting dressed or writing a check, may be problematic.

In two studies, children with FAS or FAE were evaluated on their abilities in planning, verbal fluency, using information held in short-term memory, using feedback to modify behavior, and set shifting (such as switching from naming animals to naming furniture and back to animals) (Goodman et al. 1998; Kodituwakku et al. 1995). The alcohol-exposed children had much more trouble performing these tasks than did the children in the control group. In one of the studies, however, the alcohol-exposed children had difficulty only with certain tasks involving memory skills; in other areas, they tested similarly to the control group children (Kodituwakku et al. 1995). Again, these findings support the conclusion that prenatal alcohol exposure targets specific areas of the brain.

In another study assessing executive functioning, teenagers and adults with FAS or FAE were able to read and write numbers as well as control subjects (Kopera-Frye et al. 1996). The individuals with FAS or FAE, however, had more difficulty in calculating and estimating magnitude. Nearly all the alcohol-exposed subjects could identify the larger of a pair of numbers (which suggests an understanding of magnitude), but they could not apply this knowledge to estimate magnitude. For example, one task consisted of questions for which most people do not know the exact answer (for example, "What is the height of the White House?"). Nearly half of the subjects with FAS or FAE could not make a reasonable estimate; for 20 percent of the subjects, this was the only task they had trouble performing. Although it is unclear to what extent these difficulties are related to lower overall intellectual ability, the results of this study support those of others documenting specific mathematical and problem-solving difficulties in persons with prenatal alcohol exposure (Goldschmidt et al. 1996; Kodituwakku et al. 1995; Mattson et al. 1996*d*; Streissguth et al. 1994*a*).

Attention

Problems in maintaining attention have long been associated with FAS and are quite common, affecting 6 in 10 children and adolescents with FAS (Nanson and Hiscock 1990; Streissguth et al. 1995, 1996). Deficits in attention have also been reported for children exposed to relatively low levels of alcohol before birth (Streissguth et al. 1995).

In one recent study, children with FAS were compared with children with attention deficit-hyperactivity disorder (ADHD) and children with neither condition (Coles et al. 1997). The first two groups performed more poorly than the control group, but they also performed differently from each other. The FAS children performed most poorly on tasks that required shifting attention from one feature of an attention stimulus to another—a function that is related to set shifting. The ADHD group had more difficulty sustaining attention over time and focusing attention in order to exclude extraneous information.

This and similar studies indicate that the attention disruption associated with prenatal alcohol exposure is different from that arising from other disorders, like ADHD. If this is indeed the case, it has important implications for diagnosing and treating attention disorders that are specifically due to prenatal alcohol exposure.

Motor Control

Studies of humans (Kyllerman et al. 1985; Streissguth et al. 1980) and animals (Goodlett et al. 1991; Hannigan and Riley 1989; Meyer et al. 1990) exposed to alcohol prenatally have consistently found impairments in the development of motor control, which directs voluntary movement. Motor control is a complex function influenced by the CNS; by the peripheral nervous system, which provides feedback to the CNS from the body's sensory organs, such as the eyes, ears, and skin; and by the vestibular system, located in the inner ear, which is involved in the sense of balance and the motor reactions used to maintain it. Because defects in any of these systems can affect motor control, researchers have attempted to separate out alcohol's effects on the different systems experimentally.

In one such effort, school-age children with a history of prenatal alcohol exposure, with or without a diagnosis of FAS, were compared with children without alcohol exposure (Roebuck et al. 1998*a*). The children were tested for their ability to maintain their balance under varying conditions, such as with open or closed eyes or while standing on a stable or a moving surface. Those with heavy prenatal alcohol exposure were able to maintain their balance under normal conditions and when the visual information was altered. But when both the visual system and the somatosensory system (which uses feedback from the skin, muscles, and joints) were challenged, the alcohol-exposed children had more difficulty than the control group children. The researchers concluded that the alcohol-exposed children were overly reliant on somatosensory information to maintain motor control over balance and were not able to use other sensory systems, such as their visual or vestibular systems, to compensate. They stated that the deficits may be related to abnormalities in the cerebellum (which is involved in movement as well as cognitive functions), as previously reported in FAS children.

In a follow-up study, researchers also examined the children's motor reactions to correct balance disruptions, an ability that relies on the vestibular system (Roebuck et al. 1998*b*). To assess this ability, the researchers disrupted the children's balance and then measured the reactions of their muscles with electromyography (EMG), a technique that uses electrical stimulation to provide feedback about the functioning of the skeletal muscles. The results revealed significant differences between the alcohol-exposed and the nonexposed children. But the differences were seen only in certain types of motor responses—specifically, those thought to involve a pathway through the brain's cerebral cortex. The EMG data thereby support the notion that balance deficits may be due to problems of the CNS rather than the peripheral nervous system. This hypothesis is also supported by related work suggesting that abnormal balance and gait in children with prenatal alcohol exposure are due to inadequate motor coordination by the CNS rather than to an impaired vestibular system (Church et al. 1997).

Effects on Mental Health and Psychosocial Behavior

Although not as extensively studied as cognitive and motor skills, the psychosocial and psychiatric effects of prenatal alcohol exposure also have profound implications for the lives of alcohol-exposed children and their families. Impaired social functioning, disturbed behaviors, and psychiatric disorders are common in people with FAS. These problems, which can occur with or without mental retardation and persist into adulthood, often disrupt daily life and magnify other FAS-related problems.

Mental Health

In a large study of secondary disabilities in persons of various ages with FAS or FAE, the great majority of the 415 participants—94 percent—were found to have a history of mental health problems (Streissguth et al. 1996). Attention deficits, as mentioned previously, were the most frequent problems in children and adolescents, reported in 61 percent of both groups. Among adults, depression was the most frequently reported problem (52 percent).

Another, smaller study also found that the proportion of subjects who had ever had a psychiatric disorder was far greater than what would be expected in the general population (Famy et al. 1998). Psychiatric interviews with 25 adults with FAS or FAE showed that 74 percent previously had psychiatric treatment; among the diagnoses were current or past alcohol or drug abuse (60 percent), major depressive disorder (44 percent), and avoidant personality disorder (29 percent).

Similar disturbances were reported in a study of 44 children with FAS whose mental health histories were tracked over 10 to 14 years (Spohr et al. 1994). The most commonly reported disorders were emotional disorders (50 percent), persistent repetition of meaningless gestures (50 percent), speech disorders (35 percent), and hyperactivity (32 percent).

Two other psychiatric disorders have received attention in FAS research: Tourette syndrome and autism. Tourette syndrome is a neurological condition characterized by tics—involuntary, sudden, repetitious movements. Researchers conducted a large survey of individuals with Tourette syndrome, some of whom also had obsessive-compulsive disorder (OCD), a psychiatric disorder in which a person engages in repetitive actions in order to relieve anxiety (Santangelo et al. 1994). The authors reported that OCD in persons with Tourette syndrome was associated with prenatal exposure to "relatively high levels" of alcohol (defined as more than two drinks per day), coffee (more than two cups per day), or cigarettes (more than 10 per day). They suggested that, for some individuals with Tourette syndrome, early brain damage, such as that caused by alcohol exposure, may play a role in the development or worsening of coexisting OCD. Although there are no other published reports of Tourette syndrome in individuals with prenatal alcohol exposure, the presence of tics was reported in over 10 percent of one study population with FAS (Spohr et al. 1994).

Autism is a developmental disorder characterized by severe social, communication, and behavioral problems, such as social withdrawal, aggression, and/or absence of or limited language. Autistic behaviors have been noted in school-age children who were exposed to alcohol prenatally (Nanson 1992) and, more recently, in younger children (Harris et al. 1995). Among the behaviors noted in these children were impairments in social interaction and communication, which are typical of autism. Autistic behaviors have also been noted in alcohol-exposed children both with and without the diagnosis of FAS.

Psychosocial Behavior

Other studies that use questionnaires and rating scales to assess social abilities and psychological functioning have indicated impairments in alcohol-exposed children. In one of these studies, the Personality Inventory for Children (PIC) was used to study children with heavy prenatal alcohol exposure, with or without FAS (Roebuck et al. 1999). The PIC measured a wide range of psychological and social measures and accomplishments of the children, as noted by their

parents. The alcohol-exposed children had significantly higher scores, indicating greater problems, than did the control group children in a number of areas, including anxiety, social skills, and academic achievement. In another study, the Child Behavior Checklist was used to score alcohol-exposed and control group children, matched for verbal IQ and other demographic variables, on a number of behavioral problem scales, such as anxiety, depression, and attention problems (Mattson and Riley 2000). Again, the alcohol-exposed children scored significantly higher than the control group children on all of the problem scales. Both studies indicate that prenatal alcohol exposure, regardless of whether it has resulted in a diagnosis of FAS, can lead to significant psychosocial impairment.

Studies have found that alcohol-exposed children have a variety of impairments in social abilities that could affect them throughout their lives. In one study, FAS children were compared with normally developing control group children and also with a separate group of control children who were matched for overall intellectual ability (Thomas et al. 1998). The children with FAS had more deficits in social skills, such as manners and interactions with others, than did the non-exposed children (Thomas et al. 1998). This difference was greater at older ages, indicating that social skills developed more slowly in the FAS children. Other studies have also found deficits in social skills among adolescents and adults with FAS or FAE (Mattson and Riley 1998; Streissguth et al. 1991).

In a recent effort to help evaluate behavioral disorders in alcohol-exposed individuals, researchers have designed a behavior scale based on data from 472 patients (Streissguth et al. 1998). The scale has been used to identify individuals with presumed or known alcohol exposure and to predict whether alcohol-exposed individuals would be able to live independently. Further testing will be required to evaluate whether the scale is sensitive enough to distinguish individuals with alcohol-related impairments from those with other developmental disorders.

In Closing

Imaging studies have demonstrated abnormalities of certain brain regions in persons exposed to alcohol prenatally, whereas other regions seem to be spared structural damage. Similarly, research shows that many neurobehavioral deficits are notably linked to prenatal alcohol exposure, while other functions appear to remain intact. These studies strongly support the notion that alcohol has specific, rather than global, effects on the developing brain.

By understanding the areas of the brain that are affected by alcohol, and how these brain changes affect behavior, researchers can work more effectively to design means of intervention and perhaps prevention. Relatively little research has been conducted in this area; there is a need for more well-designed studies that focus on brain-behavior correlations. Future research can draw from an extraordinary body of literature based on nearly three decades of research using animal models.

Although research in animals and humans is continuing to provide details about alcohol-induced deficits, efforts to prevent or ameliorate the effects of alcohol exposure are not nearly as advanced. Research on effective prevention strategies is critical to reducing the impact of prenatal alcohol exposure (see the section "Issues in Fetal Alcohol Syndrome Prevention" later in this chapter).

What we do know, however, is that prenatal alcohol exposure can cause specific, irreversible brain damage that can have a devastating impact on affected individuals, their caretakers, and society. These brain and behavior changes are seen in children with heavy prenatal alcohol exposure both with and without the facial features necessary for a diagnosis of FAS. Future research focusing on the diagnostic categories of ARBD and ARND will greatly expand our knowledge of alcohol's effects on the developing CNS and allow better, more appropriate intervention strategies for the full spectrum of alcohol-related effects.

References

Chandler, L.S.; Richardson, G.A.; Gallagher, J.D.; and Day, N.L. Prenatal exposure to alcohol and marijuana: Effects on motor development of preschool children. *Alcohol Clin Exp Res* 20(3): 455–461, 1996.

Church, M.W.; Eldis, F.; Blakley, B.W.; and Bawle, E.V. Hearing, language, speech, vestibular, and dentofacial disorders in fetal alcohol syndrome. *Alcohol Clin Exp Res* 21(2):227–237, 1997.

Clarren, S.K. Neuropathology in fetal alcohol syndrome. In: West, J.R., ed. *Alcohol and Brain Development.* New York, NY: Oxford University Press, 1986. pp. 158–166.

Clarren, S.K., and Smith, D.W. Fetal alcohol syndrome. *N Engl J Med* 298(19):1063–1067, 1978.

Coles, C.D.; Platzman, K.A.; Raskind-Hood, C.L.; Brown, R.T.; Falek, A.; and Smith, I.E. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol Clin Exp Res* 21(1):150–161, 1997.

Famy, C.; Streissguth, A.P.; and Unis, A.S. Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. *Am J Psychiatry* 155(4): 552–554, 1998.

Fried, P.A., and Watkinson, B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J Dev Behav Pediatr* 11(2):49–58, 1990.

Goldschmidt, L.; Richardson, G.A.; Stoffer, D.S.; Geva, D.; and Day, N.L. Prenatal alcohol exposure and academic achievement at age six: A nonlinear fit. *Alcohol Clin Exp Res* 20(4):763–770, 1996.

Goodlett, C.R.; Marcussen, B.L.; and West, J.R. A single day of alcohol exposure during the brain growth spurt induces brain weight restriction and cerebellar Purkinje cell loss. *Alcohol* 7(2):107–114, 1990.

Goodlett, C.R.; Thomas, J.D.; and West, J.R. Long-term deficits in cerebellar growth and rotarod performance of rats following "binge-like" alcohol exposure during the neonatal brain growth spurt. *Neurotoxicol Teratol* 13(1):69–74, 1991.

Goodman, A.M.; Mattson, S.N.; Caine, C.; Delis, D.C.; and Riley, E.P. Executive functioning in children exposed to alcohol prenatally. *Alcohol Clin Exp Res* 22(3):61A, 1998.

Gordis, E. *Alcohol Research: Promise for the Decade.* Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, 1991.

Hannigan, J.H., and Riley, E.P. Prenatal ethanol alters gait in rats. *Alcohol* 5(6):451–454, 1989.

Harris, S.R.; MacKay, L.L.; and Osborn, J.A. Autistic behaviors in offspring of mothers abusing alcohol and other drugs: A series of case reports. *Alcohol Clin Exp Res* 19(3):660–665, 1995.

Harris-Collazo, M.R.; Kwok, W.; Mattson, S.N.; Jernigan, S.N.; and Riley, E.P. Quantitative magnetic resonance imaging analysis of fetal alcohol syndrome. *J Int Neuropsychol Soc* 4(1): 48, 1998.

Holzman, C.; Paneth, N.; Little, R.; and Pinto-Martin, J. Perinatal brain injury in premature infants born to mothers using alcohol in pregnancy: Neonatal Brain Hemorrhage Study Team. *Pediatrics* 95(1):66–73, 1995.

Hunt, E.; Streissguth, A.P.; Kerr, B.; and Olson, H.C. Mothers' alcohol consumption during pregnancy: Effects on spatial-visual reasoning in 14-year-old children. *Psychol Sci* 6(6):339–342, 1995.

Jacobson, S.W.; Jacobson, J.L.; and Sokol, R.J. Effects of fetal alcohol exposure on infant reaction time. *Alcohol Clin Exp Res* 18(5):1125–1132, 1994.

Janzen, L.A.; Nanson, J.L.; and Block, G.W. Neuropsychological evaluation of preschoolers with fetal alcohol syndrome. *Neurotoxicol Teratol* 17(3):273–279, 1995.

Johnson, V.P.; Swayze, V.W. II; Sato, Y.; and Andreasen, N.C. Fetal alcohol syndrome: Craniofacial and central nervous system manifestations. *Am J Med Genet* 61(4):329–339, 1996.

Jones, K.L., and Smith, D.W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2(7836):999–1001, 1973.

Jones, K.L.; Smith, D.W.; Ulleland, C.N.; and Streissguth, A.P. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1(7815):1267–1271, 1973.

Kaneko, W.M.; Ehlers, C.L.; Philips, E.L.; and Riley, E.P. Auditory event-related potentials in fetal alcohol syndrome and Down's syndrome children. *Alcohol Clin Exp Res* 20(1):35–42, 1996*a*.

Kaneko, W.M.; Phillips, E.L.; Riley, E.P.; and Ehlers, C.L. EEG findings in fetal alcohol syndrome and Down syndrome children. *Electroencephalogr Clin Neurophysiol* 98(1):20–28, 1996*b*.

Kodituwakku, P.W.; Handmaker, N.S.; Cutler, S.K.; Weathersby, E.K.; and Handmaker, S.D. Specific impairments in self-regulation in children exposed to alcohol prenatally. *Alcohol Clin Exp Res* 19(6):1558–1564, 1995.

Kopera-Frye, K.; Dehaene, S.; and Streissguth, A.P. Impairments of number processing induced by prenatal alcohol exposure. *Neuropsychologia* 34(12):1187–1196, 1996.

Kyllerman, M.; Aronson, M.; Sabel, K.G.; Karlberg, E.; Sandin, B.; and Olegard, R. Children of alcoholic mothers: Growth and motor performance compared to matched controls. *Acta Paediatr Scand* 74:20–26, 1985.

Larroque, B.; Kaminski, M.; Dehaene, P.; Subtil, D.; Delfosse, M.J.; and Querleu, D. Moderate prenatal alcohol exposure and psychomotor development at preschool age. *Am J Public Health* 85(12):1654–1661, 1995.

Lemoine, P.; Harousseau, H.; Borteyru, J.P.; and Menuet, J.C. Les enfants de parents alcooliques: Anomalies observees a proposos de 127 cas [Children of alcoholic parents: Abnormalities observed in 127 cases]. *Ouest Med* 21(6): 476–482, 1968.

Lezak, M.D. *Neuropsychological Assessment*, 3rd ed. New York, NY: Oxford University Press, 1995.

Mattson, S.N.; Gramling, L.; Delis, D.C.; Jones, K.L.; and Riley, E.P. Global-local processing in children prenatally exposed to alcohol. *Child Neuropsychol* 2(3):165–175, 1996*a*.

Mattson, S.N., and Riley, E.P. Brain anomalies in fetal alcohol syndrome. In: Abel, E.A., ed. *Fetal Alcohol Syndrome: From Mechanism to Prevention.* Boca Raton, FL: CRC Press, 1996. pp. 51-68.

Mattson, S.N., and Riley, E.P. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcohol Clin Exp Res* 22(2):279–294, 1998.

Mattson, S.N., and Riley, E.P. Implicit and explicit memory functioning in children with heavy prenatal alcohol exposure. *J Int Neuropsychol Soc* 5(5):462–471, 1999.

Mattson, S.N., and Riley, E.P. Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls. *Alcohol Clin Exp Res*, in press.

Mattson, S.N.; Riley, E.P.; Delis, D.C.; Stern, C.; and Jones, K.L. Verbal learning and memory in children with fetal alcohol syndrome. *Alcohol Clin Exp Res* 20(5):810–816, 1996*b*.

Mattson, S.N.; Riley, E.P.; Gramling, L.; Delis, D.C.; and Jones, K.L. Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome. *Neuropsychology* 12(1):146–153, 1998.

Mattson, S.N.; Riley, E.P.; Jernigan, T.L.; Ehlers, C.L.; Delis, D.C.; Jones, K.L.; Stern, C.; Johnson, K.A.; Hesselink, J.R.; and Bellugi, U. Fetal alcohol syndrome: A case report of neuropsychological, MRI, and EEG assessment of two children. *Alcohol Clin Exp Res* 16(5):1001–1003, 1992.

Mattson, S.N.; Jernigan, T.L.; and Riley, E.P. MRI and prenatal alcohol exposure: Images provide insight into FAS. *Alcohol Health Res World* 18(1):49–52, 1994*a*.

Mattson, S.N.; Riley, E.P.; Jernigan, T.L.; Garcia, A.; Kaneko, W.M.; Ehlers, C.L.; and Jones, K.L. A decrease in the size of the basal ganglia following prenatal alcohol exposure: A preliminary report. *Neurotoxicol Teratol* 16(3): 283–289, 1994*b*.

Mattson, S.N.; Riley, E.P.; Sowell, E.R.; Jernigan, T.L.; Sobel, D.F.; and Jones, K.L. A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcohol Clin Exp Res* 20(6): 1088–1093, 1996*c*.

Mattson, S.N.; Roebuck, T.M.; and Riley, E.P. Wisconsin card sorting performance in children prenatally exposed to alcohol. *Alcohol Clin Exp Res* 20:74A, 1996*d*.

Meyer, L.S.; Kotch, L.E.; and Riley, E.P. Neonatal ethanol exposure: Functional alterations associated with cerebellar growth retardation. *Neurotoxicol Teratol* 12(1):15–22, 1990.

Nanson, J.L. Autism in fetal alcohol syndrome: A report of six cases. *Alcohol Clin Exp Res* 16(3):558–565, 1992.

Nanson, J.L., and Hiscock, M. Attention deficits in children exposed to alcohol prenatally. *Alcohol Clin Exp Res* 14(5):656–661, 1990.

National Institute on Alcohol Abuse and Alcoholism. *Ninth Special Report to the U.S. Congress on Alcohol and Health.* NIH Publication No. 97-4017. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 1997.

Nugent, J.K.; Lester, B.M.; Greene, S.M.; Wieczorek-Deering, D.; and O'Mahony, P. The effects of maternal alcohol consumption and cigarette smoking during pregnancy on acoustic cry analysis. *Child Dev* 67(4):1806–1815, 1996.

Richardson, G.A.; Day, N.L.; and Goldschmidt, L. Prenatal alcohol, marijuana, and tobacco use: Infant mental and motor development. *Neurotoxicol Teratol* 17(4):479–487, 1995.

Riikonen, R.S. Difference in susceptibility to teratogenic effects of alcohol in discordant twins exposed to alcohol during the second half of gestation. *Pediatr Neurol* 11(4):332–336, 1994.

Riley, E.P.; Mattson, S.N.; Sowell, E.R.; Jernigan, T.L.; Sobel, D.F.; and Jones, K.L. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcohol Clin Exp Res* 19(5): 1198–1202, 1995.

Robin, N.H., and Zackai, E.H. Unusual craniofacial dysmorphia due to prenatal alcohol and cocaine exposure. *Teratology* 50(2):160–164, 1994.

Roebuck, T.M.; Mattson, S.N.; and Riley, E.P. Behavioral and psychosocial profiles of alcohol-exposed children. *Alcohol Clin Exp Res* 23(6): 1070–1076, 1999.

Roebuck, T.M.; Simmons, R.W.; Mattson, S.N.; and Riley, E.P. Prenatal exposure to alcohol affects the ability to maintain postural balance. *Alcohol Clin Exp Res* 22(1):252–258, 1998*a*.

Roebuck, T.M.; Simmons, R.W.; Richardson, C.; Mattson, S.N.; and Riley, E.P. Neuromuscular responses to disturbance of balance in children with prenatal exposure to alcohol. *Alcohol Clin Exp Res* 22(9):1992–1997, 1998*b*.

Santangelo, S.L.; Pauls, D.L.; Goldstein, J.M.; Faraone, S.V.; Tsuang, M.T.; and Leckman, J.F. Tourette's syndrome: What are the influences of gender and comorbid obsessive-compulsive disorder? *J Am Acad Child Adolesc Psychiatry* 33(6):795–804, 1994.

Shaw, G.M.; Velie, E.M.; and Morland, K.B. Parental recreational drug use and risk for neural tube defects. *Am J Epidemiol* 144(12):1155–1160, 1996.

Sowell, E.R.; Jernigan, T.L.; Mattson, S.N.; Riley, E.P.; Sobel, D.F.; and Jones, K.L. Abnormal development of the cerebellar vermis in children prenatally exposed to alcohol: Size reduction in lobules I–V. *Alcohol Clin Exp Res* 20(1):31–34, 1996.

Spohr, H.L.; Willms, J.; and Steinhausen, H.C. The fetal alcohol syndrome in adolescence. *Acta Pediatr* 404(supp.):19–26, 1994.

Stratton, K.; Howe, C.; and Battaglia, F., eds. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment.* Washington, DC: National Academy Press, 1996.

Streissguth, A.P.; Aase, J.M.; Clarren, S.K.; Randels, S.P.; LaDue, R.A.; and Smith, D.F. Fetal alcohol syndrome in adolescents and adults. *JAMA* 265(15):1961–1967, 1991.

Streissguth, A.P.; Barr, H.M.; Kogan, J.; and Bookstein, F.L. *Understanding the Occurrence of Secondary Disabilities in Clients With Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE): Final Report.* Seattle, WA: University of Washington School of Medicine, Department of Psychiatry and Behavioral Sciences, Fetal Alcohol and Drug Unit, 1996.

Streissguth, A.P.; Barr, H.M.; Martin, D.C.; and Herman, C.S. Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months. *Alcohol Clin Exp Res* 4(2):152–164, 1980.

Streissguth, A.P.; Barr, H.M.; Olson, H.C.; Sampson, P.D.; Bookstein, F.L.; and Burgess, D.M. Drinking during pregnancy decreases word attack and arithmetic scores on standardized tests: Adolescent data from a population-based prospective study. *Alcohol Clin Exp Res* 18(2): 248–254, 1994*a*.

Streissguth, A.P.; Bookstein, F.L.; Barr, H.M.; Press, S.; and Sampson, P.D. A fetal alcohol behavior scale. *Alcohol Clin Exp Res* 22(2): 325–333, 1998.

Streissguth, A.P.; Bookstein, F.L.; Sampson, P.D.; and Barr, H.M. Attention: Prenatal alcohol and continuities of vigilance and attentional problems from 4 through 14 years. *Dev Psychopathol* 7(5): 419–446, 1995.

Streissguth, A.P.; Sampson, P.D.; Olson, H.C.; Bookstein, F.L.; Barr, H.M.; Scott, M.; Feldman, J.; and Mirsky, A.F. Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring—A longitudinal prospective study. *Alcohol Clin Exp Res* 18(1):202–218, 1994*b*.

Swayze, V.W. II; Johnson, V.P.; Hanson, J.W.; Piven, J.; Sato, Y.; Giedd, J.N.; Mosnik, D.; and Andreasen, N.C. Magnetic resonance imaging of brain anomalies in fetal alcohol syndrome. *Pediatrics* 99(2):232–240, 1997.

Thomas, S.E.; Kelly, S.J.; Mattson, S.N.; and Riley, E.P. Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls. *Alcohol Clin Exp Res* 22(2):528–533, 1998.

Uecker, A., and Nadel, L. Spatial locations gone awry: Object and spatial memory deficits in children with fetal alcohol syndrome. *Neuropsychologia* 34(3):209–223, 1996.

Zeskind, P.S.; Platzman, K.; Coles, C.D.; and Schuetze, P.A. Cry analysis detects subclinical effects of prenatal alcohol exposure in newborn infants. *Infant Behav Dev* 19(4):497–500, 1996.